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(54) FORME POLYMORPHE DE L'HYDROGENOSULFATE DE CLOPIDOGREL

(54) POLYMORPHIC CLOPIDOGREL HYDROGENESULPHATE FORM

(57) Nouveau polymorphe orthorhombique de l'hydrogénosulfate de clopidogrel ou hydrogénosulfate de (+)-(S)-α-(2-chlorophényl) -4,5,6,7-tétrahydrothiéno [3,2-c] pyridinyl-5- acétate de méthyle et un procédé pour sa préparation.

(57) The invention relates to a novel polymorphic orthorhombic hydrogenosulphate or (+)-(S)-α-(2 -chlorophenyl) -4,5,6,7- tetrahydrothieno [3,2-c] pyridinyl-5-methyl acetate hydrogenosulphate form and to a method for the production thereof.

Abstract

The invention relates to a novel polymorphic orthorhombic hydrogenosulphate or (+)-(S)-α-(2 -chlorophenyl) -4,5,6,7-tetrahydrothieno [3,2-c] pyridinyl-5-methyl acetate hydrogenosulphate form and to a method for the production thereof

Polymorphic form of clopidogrel hydrogen sulphate

The present invention relates to a novel polymorph of clopidogrel hydrogen sulphate or methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridinyl-5-acetate hydrogen sulphate and to a method for its preparation. More particularly, the invention relates to the preparation of this polymorph called Form 2 and to the isolation of this compound in this novel crystalline form, as well as to the pharmaceutical compositions containing it.

Clopidogrel hydrogen sulphate is an antithrombotic which was described for the first time in EP 281459. The method of synthesis claimed in this patent allows the preparation of clopidogrel hydrogen sulphate which will be called Form 1. It has now been discovered that clopidogrel hydrogen sulphate can exist in different polymorphic crystalline forms which differ from each other in their stability, in their physical properties, in their spectral characteristics and in their method of preparation.

Thus, one of these novel polymorphic forms is the subject of the present invention; it is described in the present application and will be termed Form 2.

The present invention also relates to a method for the preparation of clopidogrel hydrogen sulphate in its polymorphic form 2.

Patent EP 281459 describes enantiomers of derivatives of tetrahydrothienopyridines and of their

pharmaceutically acceptable salts. EP 281459 specifically claims clopidogrel hydrogen sulphate, that is to say the dextrorotatory isomer, which possesses excellent anti-platelet aggregation activity whereas the levorotatory isomer is less active and less well tolerated.

Patent EP 281459, filed ten years ago, makes no reference to the existence of specific polymorphic forms of clopidogrel hydrogen sulphate. The synthesis described in EP 281459 allows the preparation of the clopidogrel polymorph hydrogen sulphate Form 1. EP 281459 does not suggest the existence of various polymorphic forms of clopidogrel or of clopidogrel hydrogen sulphate either.

According to all the teachings of the above documents, the dextrorotatory isomer of clopidogrel is prepared by salification of the racemic compound with an optically active acid such as 10-L-camphorsulphonic acid in acetone followed by successive recrystallizations of the salt until a product with a constant optical rotation is obtained, followed by the release of the dextrorotatory isomer from its salt by a base. Clopidogrel hydrogen sulphate is then obtained in a conventional manner by dissolving the said base in acetone cooled on ice and adding concentrated sulphuric acid until precipitation occurs. The precipitate thus obtained is then isolated by filtration, washed and

dried to give clopidogrel hydrogen sulphate in the form of white crystals whose melting point is 184°C and whose optical rotation is +55.1° (c = 1.891/CH_3OH).

The methods of synthesis described in the prior art allow only the synthesis of clopidogrel hydrogen sulphate Form 1.

Thus, the present invention relates to the polymorphic form, termed Form 2, of clopidogrel hydrogen sulphate, which like Form 1 of this compound is useful as a medicament for the prophylaxis and the treatment of thrombosis by acting as a platelet aggregation inhibitor. As regards the use of clopidogrel and of its salts, reference may be made to Drugs of the Future 1993, 18, *2*, 107-112. Clopidogrel hydrogen sulphate polymorph Form 2 is therefore used as active ingredient for the preparation of a medicament, in combination with at least one pharmaceutically acceptable excipient, in the same indications as Form 1.

It has now been found that if clopidogrel hydrogen sulphate is crystallized from a solvent, it is possible to obtain either the crystalline form corresponding to that of the product obtained according to EP 281459 cited above, Form 1, or a novel, very stable, crystalline form having a well-defined structure, designated hereinafter Form 2. More particularly, it has been found that the novel

crystalline form of clopidogrel hydrogen sulphate, Form 2, is at least as stable as the Form 1 described and that it does not spontaneously convert to the previously known Form 1. Furthermore, the powder obtained from Form 2 is more compact and a lot less electrostatic than that obtained from Form 1 and can therefore be more easily subjected to any treatment under the usual conditions of pharmaceutical technology and in particular of industrial galenic pharmacology.

It has, moreover, been observed that Form 2 exhibits a lower solubility than Form 1 resulting from its higher thermodynamic stability.

The difference between the novel crystalline form of clopidogrel hydrogen sulphate according to the present invention, Form 2 and Form 1 is evident from an examination of Figures 1 to 4, whereas Figures 5 to 7 show the structure in the crystals of Form 2.

Figures 1 to 7 are characterized as follows:

- **Figure 1** gives the X-ray diffractogram of clopidogrel hydrogen sulphate Form 1 powder;
- **Figure 2** shows the X-ray diffractogram of clopidogrel hydrogen sulphate Form 2 powder;
- **Figure 3** shows the infrared spectrum of Form 2;
- **Figure 4** shows the infrared spectrum of Form 1;
- **Figure 5** shows the structural formula of clopidogrel hydrogen sulphate with numbering of the atoms in the crystalline Form 2;

- **Figure 6** shows the spatial conformation of clopidogrel hydrogen sulphate Form 2;
- **Figure 7** shows the stacking of the clopidogrel hydrogen sulphate Form 2 molecules in the mesh of the crystal.

It has been observed, from the crystallographic data, that the crystalline structure of Form 1 contains two free cations in the clopidogrel crystal and two free bisulphate anions. The two free cations are of a similar conformation.

According to the crystallographic data for Form 2, it has been observed that it contains a free cation in the crystal-bisulphate anion pair.

In the two forms, the cations are axially protonated and the nitrogen atom is of R configuration; the conformation of the cations in Form 2 is different from that observed in Form 1.

In the molecular arrangement of the two crystalline forms, no site is occupied by solvent molecules.

The arrangement of the anions is very different from one to the other of the two crystalline structures. The crystalline structure of Form 2, of the orthorhombic type, is less dense (1.462 g/cm^3) than the crystalline structure of Form 1, of the monoclinic type, (1.505 g/cm^3).

According to another of its aspects, the subject of the present invention is a method for the preparation of clopidogrel hydrogen sulphate Form 2 characterized in that:

(a) methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate is dissolved in an organic solvent,

(b) camphorsulphonic acid is extracted with an aqueous alkaline solution of potassium carbonate and washed with water,

(c) the organic phase is concentrated under vacuum and the concentration residue is taken up in acetone,

(d) 80% sulphuric acid is added,

(e) the mixture is heated under reflux, the product crystallizes, the mixture is cooled, filtered and the crystals are washed and then dried under reduced pressure to give clopidogrel hydrogen sulphate Form 1,

(f) the resulting aqueous-acetone mother liquors subsequently release, after 3 to 6 months, crystals of clopidogrel hydrogen sulphate Form 2.

Thus, the present invention relates to a method for the preparation of (+)-(S)-clopidogrel hydrogen sulphate Form 2, characterized in that: The aqueous-acetone mother liquors resulting from the crystallization of (+)-(S)-clopidogrel hydrogen

sulphate Form 1 subsequently release, after 3 to 6 months, crystals of clopidogrel hydrogen sulphate Form 2.

The aqueous-acetone mother liquors resulting from the crystallization of (+)-(S)-clopidogrel hydrogen sulphate Form 1 contain from 0.3 to 1% of water.

They contain up to about 10% of clopidogrel hydrogen sulphate, this quantity being calculated from the quantity of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate used during the conversion to hydrogen sulphate.

These aqueous-acetone mother liquors release slowly, after a period of three to six months, at a temperature of less than 40°C, clopidogrel hydrogen sulphate Form 2.

According to another of its aspects, the present invention relates to another method for the preparation of clopidogrel hydrogen sulphate Form 2, characterized in that:

(a) methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate is dissolved in an organic solvent,

(b) camphorsulphonic acid is extracted with an aqueous alkaline solution of potassium carbonate and washed with water,

(c) the organic phase is concentrated under vacuum and the concentration residue is taken up in acetone,

(d) 96% sulphuric acid at 20°C is added and the mixture is seeded with clopidogrel hydrogen sulphate Form 2,

(e) the product crystallizes, the mixture is cooled, filtered and the crystals are washed and then dried under reduced pressure to give clopidogrel hydrogen sulphate Form 2.

Another alternative consists in subjecting the crystalline suspension to mechanical shearing with the aid of a shearing device. This device can reach a rotating speed of about 10,000 to 15,000 revolutions per minute. Devices having these characteristics are for example of the Turrax® type marketed by IKA-Werke (DE). These devices are moreover suitable for the treatment of industrial quantities.

The principle is to obtain, by grinding, fine particles from a base solution containing only a fraction of the total sulphuric acid. The remaining portion will then be poured in slowly in order to promote crystalline growth. Trials were carried out starting with 10% of the required sulphuric acid poured in at the beginning.

Thus, the subject of the present invention is clopidogrel hydrogen sulphate Form 2, characterized by the X-ray diffraction profile of the powder given in TABLE I.

More particularly, Form 2 is also characterized by a melting point, determined by differential enthalpy analysis (DSC), of 176°C and by characteristic absorptions in the infrared region and in the near-infrared region.

Some physical properties and the behaviour of the novel crystalline form of clopidogrel hydrogen sulphate according to the present invention are completely different from those of Form 1 as has been demonstrated by examining the two forms by conventional methods and techniques.

The X-ray diffraction profile of the powder (diffraction angle) was established with a Siemens D500TT diffractometer. The characteristic powder diffractograms between 2 and 40° at Bragg 2θ (2 theta, deg., for CuKα, λ=1.542 Å) are presented in Figure 1 for Form 1 and in Figure 2 for Form 2. The significant lines in Figure 1 are assembled in TABLE II, whereas those in Figure 2 are assembled in TABLE I.

In TABLES I and II, d is the interlattice distance and I/I_0 represents the relative intensity, expressed as a percentage of the most intense line.

TABLE I: Form 2

Significant lines in Figure 2

d(Å)	I/I_0
4.11	100.0
6.86	61.7
3.87	61.4
3.60	56.3
4.80	55.8
5.01	44.4
3.74	37.9
6.49	33.1
5.66	29.8

TABLE II: Form 1

Significant lines in Figure 1

d(Å)	I/I_0
9.60	100.0
3.49	58.8
3.83	52.0
3.80	42.5
4.31	39.0
8.13	37.2
4.80	25.5
3.86	19.1
5.80	16.8
4.95	16.8

Differential enthalpy analysis (DSC) of Forms 1 and 2 was carried out comparatively using a Perkin Elmer DSC 7 apparatus, calibrated with reference to indium. For the calorimetric analysis, there were used 2.899 mg of Form 1 or 2.574 mg of Form 2, as obtained in EXAMPLE 2, in a crimped and perforated aluminium cup, in a temperature range of 40 to 230°C at a heating rate of 10°C/minute. The melting point and the enthalpy of fusion are indicated in TABLE III. The melting point corresponds to the characteristic melting temperature obtained by DSC. This value can also be defined as being the temperature corresponding to the intersection between the base line and tangent to the rising peak of melts observed by DSC.

TABLE III

Melting point and enthalpy

	Form 1	**Form 3**
Melting point (°C)	181.2	176.0
Enthalpy of fusion (J/g)	77	87

The difference between the novel Form 2 and Form 1 of clopidogrel hydrogen sulphate was also demonstrated by infrared spectroscopy. The Fourier Transform IR (FTIR) spectra were obtained with a Perkin Elmer system 2000 spectrometer with a resolution of 4 cm^{-1} from 4000 cm^{-1} to 400 cm^{-1}. The samples are

provided in the form of pellets of KBr at 0.3% as Form 1 or as Form 2. The pellet was compressed at 10 tons for 2 minutes. Each sample was examined after 4 accumulations.

Comparison of the characteristic lines, in terms of wavelength (in cm^{-1}) and of intensity (as percentage of transmittance) is illustrated in TABLE IV.

TABLE IV

Infrared spectrum

Form 1		**Form 2**	
Wavelength (cm^{-1})	% transmittance	Wavelength (cm^{-1})	% transmittance
2987	42	2551	43
1753	14	1753	13.4
1222	16	1497	63.7
1175	12	1189	18
841	40	1029	33.2

It is evident from TABLE IV that Form 2 exhibits characteristic absorptions at 2551 cm^{-1}, 1497 cm^{-1}, 1189 cm^{-1} and 1029 cm^{-1} which are absent from Form 1.

The special structure of the powder of Form 2 was demonstrated by analysis of the monocrystal by X-ray diffraction of the powder using an MSC-Rigaka

AFC6S diffractometer and the SHELXS-90 and SHELXS-93 software on an SG IRIS Indigo work station. The position of the C-H hydrogens was generated at a distance of 0.95 Å. The crystallographic data, in particular the interplanar distances (a,b,c), the angles (α,β,γ) and the volume of each unit cell, are indicated in TABLE V.

TABLE V

Crystallographic data and establishment of the structure of Form 2

Spatial group crystalline system	**Orthorhombic $P2_12_12_1$**
Dimensions of the unit cell:	
a	10.321 (6) Å
b	20.118 (9) Å
c	9.187 (7) Å
α	90 degrees
β	90 degrees
γ	90 degrees
volume	1908 (2) $Å^3$
Z	4
density (calculated)	1.462 g/cm^3
collected reflections	2134
Factor R	0.0473

The atomic coordinates of Form 2 are given in TABLE VI, the length of the bonds in TABLE VII, the

angles between the bonds in TABLE VIII and the characteristic angles of twist in TABLE IX.

TABLE VI

Position parameters of Form 2

atom	x	y	z	U(eq)
Cl(1)	0.2223(3)	0.21728(12)	0.4295(3)	0.0835(8)
S(1)	0.8085(2)	-0.00068(11)	0.3557(3)	0.0724(7)
S(2)	0.2840(2)	0.01908(8)	0.0013(2)	0.0412(4)
O(1)	0.3030(7)	0.2376(3)	-0.0528(7)	0.087(2)
O(2)	0.4630(6)	0.1637(3)	-0.0860(6)	0.060(2)
O(3)	0.2175(6)	-0.0350(3)	0.0957(6)	0.0551(14)
O(4)	0.2728(6)	-0.0093(3)	-0.1432(5)	0.074(2)
O(5)	0.4174(4)	0.0241(2)	0.0497(6)	0.0503(13)
O(6)	0.2146(5)	0.0800(2)	0.0199(7)	0.065(2)
N(5)	0.4936(6)	0.1343(3)	0.1946(7)	0.0380(14)
C(2)	0.9111(10)	0.0427(5)	0.2500(13)	0.081(3)
C(3A)	0.7214(7)	0.1002(3)	0.2215(9)	0.047(2)
C(3)	0.8554(8)	0.0950(5)	0.1824(11)	0.060(2)
C(4)	0.6332(7)	0.1548(4)	0.1706(10)	0.044(2)
C(6)	0.4750(8)	0.1100(4)	0.3487(9)	0.045(2)
C(7)	0.5487(8)	0.0450(4)	0.3722(10)	0.051(2)
C(7A)	0.6833(8)	0.0526(3)	0.3144(9)	0.050(2)
C(8)	0.3940(8)	0.1880(4)	0.1574(9)	0.043(2)
C(9)	0.4119(7)	0.2523(3)	0.2360(9)	0.044(2)
C(10)	0.3435(8)	0.2688(4)	0.3613(10)	0.057(2)
C(11)	0.3630(10)	0.3292(4)	0.4290(11)	0.076(3)
C(12)	0.4545(10)	0.3734(4)	0.3773(12)	0.080(3)
C(13)	0.5223(10)	0.3579(4)	0.2550(12)	0.067(3)
C(14)	0.5019(8)	0.2980(3)	0.1863(10)	0.052(2)
C(15)	0.3823(8)	0.1995(4)	-0.0079(11)	0.053(2)
C(16)	0.4462(16)	0.1687(6)	-0.2422(11)	0.096(4)

TABLE VII

Intramolecular distances in Form 2

Atom	atom	distance
Cl(1)	C(10)	1.742(8)
S(1)	C(2)	1.682(12)
S(1)	C(7A)	1.722(8)
S(2)	O(6)	1.429(5)
S(2)	O(4)	1.450(5)
S(2)	O(5)	1.450(5)
S(2)	O(3)	1.551(5)
O(1)	C(15)	1.195(9)
O(2)	C(15)	1.314(10)
O(2)	C(16)	1.448(10)
N(5)	C(6)	1.510(10)
N(5)	C(4)	1.515(9)
N(5)	C(8)	1.530(9)
C(2)	C(3)	1.350(13)
C(3A)	C(7A)	1.341(10)
C(3A)	C(3)	1.432(10)
C(3A)	C(4)	1.501(10)
C(6)	C(7)	1.528(10)
C(7)	C(7A)	1.495(11)
C(8)	C(9)	1.493(10)
C(8)	C(15)	1.541(12)
C(9)	C(14)	1.384(10)
C(9)	C(10)	1.390(11)
C(10)	C(11)	1.379(11)
C(11)	C(12)	1.382(12)
C(12)	C(13)	1.359(13)
C(13)	C(14)	1.378(11)

The distances are in Ångstroms. The standard deviations estimated on the decimal are in brackets.

TABLE VIII

Angles between the intramolecular bonds involving non-hydrogen atoms

atom	Atom	atom	angle
C(2)	S(1)	C(7A)	91.2(4)
O(6)	S(2)	O(4)	114.0(4)
O(6)	S(2)	O(5)	112.3(3)
O(4)	S(2)	O(5)	112.6(3)
O(6)	S(2)	O(3)	108.2(3)
O(4)	S(2)	O(3)	101.6(3)
O(5)	S(2)	O(3)	107.3(3)
C(15)	O(2)	C(16)	115.3(9)
C(6)	N(5)	C(4)	110.1(6)
C(6)	N(5)	C(8)	110.6(6)
C(4)	N(5)	C(8)	114.5(5)
C(3)	C(2)	S(1)	113.7(7)
C(7A)	C(3A)	C(3)	113.0(8)
C(7A)	C(3A)	C(4)	122.8(7)
C(3)	C(3A)	C(4)	124.1(8)
C(2)	C(3)	C(3A)	110.7(9)
C(3A)	C(4)	N(5)	109.5(6)
N(5)	C(6)	C(7)	110.2(7)
C(7A)	C(7)	C(6)	108.9(6)
C(3A)	C(7A)	C(7)	124.9(7)
C(3A)	C(7A)	S(1)	111.4(6)
C(7)	C(7A)	S(1)	123.7(6)
C(9)	C(8)	N(5)	114.9(6)
C(9)	C(8)	C(15)	110.9(6)
N(5)	C(8)	C(15)	112.2(7)
C(14)	C(9)	C(10)	117.1(7)
C(14)	C(9)	C(8)	119.9(8)
C(10)	C(9)	C(8)	123.0(7)

TABLE VIII (continued)

Angles between the intramolecular bonds involving non-hydrogen atoms

atom	atom	atom	angle
C(11)	C(10)	C(9)	120.7(8)
C(11)	C(10)	Cl(1)	117.8(7)
C(9)	C(10)	Cl(1)	121.4(6)
C(10)	C(11)	C(12)	120.7(9)
C(13)	C(12)	C(11)	119.3(9)
C(12)	C(13)	C(14)	120.0(9)
C(13)	C(14)	C(9)	122.2(9)
O(1)	C(15)	O(2)	126.7(9)
O(1)	C(15)	C(8)	119.3(9)
O(2)	C(15)	C(8)	114.0(7)

The angles are in degrees. The standard deviations estimated on the last decimal are in brackets.

TABLE IX

Angles of conformation and characteristic twist

(1)	(2)	(3)	(4)	angle
C(7A)	S(1)	C(2)	C(3)	-1.1(9)
S(1)	C(2)	C(3)	C(3A)	0.9(12)
C(7A)	C(3A)	C(3)	C(2)	0.0(12)
C(4)	C(3A)	C(3)	C(2)	177.1(8)
C(7A)	C(3A)	C(4)	N(5)	-19.7(11)
C(3)	C(3A)	C(4)	N(5)	163.4(8)
C(6)	N(5)	C(4)	C(3A)	50.2(8)
C(8)	N(5)	C(4)	C(3A)	175.7(7)
C(4)	N(5)	C(6)	C(7)	-67.3(8)
C(8)	N(5)	C(6)	C(7)	165.0(6)
N(5)	C(6)	C(7)	C(7A)	47.8(9)
C(3)	C(3A)	C(7A)	C(7)	-179.1(8)
C(4)	C(3A)	C(7A)	C(7)	3.8(13)

TABLE IX (continued)

Angles of conformation and characteristic twist

(1)	(2)	(3)	(4)	angle
C(3)	C(3A)	C(7A)	S(1)	-0.8(9)
C(4)	C(3A)	C(7A)	S(1)	-177.9(6)
C(6)	C(7)	C(7A)	C(3A)	-17.6(12)
C(6)	C(7)	C(7A)	S(1)	164.3(6)
C(2)	S(1)	C(7A)	C(3A)	1.1(7)
C(2)	S(1)	C(7A)	C(7)	179.4(8)
C(6)	N(5)	C(8)	C(9)	68.9(8)
C(4)	N(5)	C(8)	C(9)	-56.3(10)
C(6)	N(5)	C(8)	C(15)	-163.2(6)
C(4)	N(5)	C(8)	C(15)	71.6(8)
N(5)	C(8)	C(9)	C(14)	81.4(9)
C(15)	C(8)	C(9)	C(14)	-47.2(10)
N(5)	C(8)	C(9)	C(10)	-97.3(9)
C(15)	C(8)	C(9)	C(10)	134.2(8)
C(14)	C(9)	C(10)	C(11)	1.9(12)
C(8)	C(9)	C(10)	C(11)	-179.4(8)
C(14)	C(9)	C(10)	Cl(1)	176.9(6)
C(8)	C(9)	C(10)	Cl(1)	-4.4(11)
C(9)	C(10)	C(11)	C(12)	-2.6(14)
Cl(1)	C(10)	C(11)	C(12)	-177.8(8)
C(10)	C(11)	C(12)	C(13)	3(2)
C(11)	C(12)	C(13)	C(14)	-2(2)
C(12)	C(13)	C(14)	C(9)	1.1(14)
C(10)	C(9)	C(14)	C(13)	-1.1(12)
C(8)	C(9)	C(14)	C(13)	-179.9(8)
C(16)	O(2)	C(15)	O(1)	-4.3(13)
C(16)	O(2)	C(15)	C(8)	174.5(8)
C(9)	C(8)	C(15)	O(1)	-54.0(10)
N(5)	C(8)	C(15)	O(1)	176.0(7)
C(9)	C(8)	C(15)	O(2)	127.1(7)
N(5)	C(8)	C(15)	O(2)	-2.8(9)

The angles are in degrees. The standard deviations estimated on the last decimal are in brackets.

The sign is positive if, when looking from atom 2 to atom 3, through a clockwise movement atom 1 is superimposed on atom 4.

X-Ray crystallography study, in particular the crystallography data of TABLE I, the atomic coordinates of TABLE VI, the bond length in TABLE VII, the angles between the bonds in TABLE VIII and the characteristic angles of twist in TABLE IX provide proof of the proposed structure illustrated in Figures 5 and 6.

Examination under a microscope revealed that the crystals of the novel Form 2 are morphologically different from those of Form 1.

The crystals of Form 1 exist in the form of irregular plates, whereas the crystals of Form 2 exist in the form of agglomerates.

By virtue of its low electrostaticity compared with that of Form 1, it is therefore particularly suitable for the manufacture of pharmaceutical compositions for the treatment of any disease in which an antithrombotic is indicated.

Thus, according to another of its aspects, the subject of the present invention is pharmaceutical compositions containing, as active ingredient,

clopidogrel hydrogen sulphate Form 2 characterized by the X-ray diffraction profile of the powder illustrated in TABLE I.

Preferably, the clopidogrel hydrogen sulphate Form 2 according to the present invention is formulated in pharmaceutical compositions for oral administration containing 75 mg of active ingredient per dosage unit, in the form of a mixture with at least one pharmaceutical excipient.

When a solid composition in the form of tablets is prepared, the principal active ingredient is mixed with a pharmaceutical carrier, such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic and the like. The tablets may be coated with sucrose or other appropriate substances or alternatively they may be processed such that they have a prolonged or delayed activity and that they continuously release a predetermined quantity of active ingredient.

A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with a diluent and pouring the mixture obtained into soft or hard gelatin capsules.

The powders or granules dispersible in water may contain the active ingredient in the form of a mixture with dispersing agents or wetting agents, or suspending agents, such as polyvinylpyrrolidone, as well as with sweeteners, or flavour correctors.

If it is desired to formulate the active ingredient for rectal administration, suppositories are used which are prepared with binders which melt at the rectal temperature, for example coco butter or polyethylene glycols.

For parenteral administration, aqueous suspensions, saline solutions or sterile and injectable solutions are used.

The active ingredient may also be formulated in the form of microcapsules, optionally with one or more carriers or additives.

The following EXAMPLES illustrate the invention without however limiting it.

Preparation of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate.

400 kg of racemic methyl α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate hydrochloride and 1840 kg of dichloromethane are loaded into a stirred reactor. 1200 kg of an 8% aqueous sodium bicarbonate solution are then slowly added. After settling out, the organic phase is concentrated under vacuum. The concentration residue is diluted with 1000 litres of acetone. A solution of 154 kg of 1 R-10 camphorsulphonic acid in 620 litres of acetone is added at 20-25°C. The methyl α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate

camphorsulphonate is cooled and crystallized, with seeding if necessary. When the crystallization is abundant, the mixture is heated under reflux and then cooled to 25°C. The crystals are then filtered and washed with acetone and then dried under reduced pressure. 196 kg of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate are thus obtained, that is a yield of 33%.

Preparation of clopidogrel hydrogen sulphate Form 2

EXAMPLE 1 A

50 g of clopidogrel camphorsulphonate prepared as indicated above are introduced into a 250 ml reactor, under nitrogen. 100 ml of dichloromethane are added and the reaction mixture is stirred for 10 minutes. Then a solution of 9.1 g of potassium carbonate dissolved in 70 ml of deionized water is introduced. The organic phase is drawn off and the aqueous phase is washed several times with dichloromethane. The organic phases are combined and concentrated under vacuum. 229 ml of acetone are added to the concentrate and the mixture is filtered on sintered material of 0.1 μ to 0.22 μ. The acetone solution containing the base is loaded into a reactor under nitrogen and 7.4 g of an 80% sulphuric acid solution are then added, at 20°C, and then the mixture

is heated until reflux begins; the crystallization starts and the reflux is maintained for 2 hours.

The solvent is distilled off, the mixture cooled to a temperature of 0 to -5°C and the crystals separated by filtration on a Büchner flask to obtain, after drying, 21.4 g of clopidogrel hydrogen sulphate Form 2; m.p. = 176 ±3°C.

EXAMPLE 1 B

1200 kg of clopidogrel camphorsulphonate prepared as indicated above are introduced into a 6000 litres reactor, under nitrogen. 2345 litres of dichloromethane are added and the reaction mixture is stirred for 30 minutes to 1 hour. Then a solution of 214.5 kg of potassium carbonate dissolved in 1827 litres of deionized water is introduced. The organic phase is drawn off and the aqueous phase is washed several times with dichloromethane. The organic phases are combined and concentrated under vacuum. Acetone is added to the concentrate and the mixture is filtered on a cartridge filter of 0.1 μ to 1 μ. The acetone solution (3033 litres) containing the base is loaded into a reactor under nitrogen and 264.8 kg of an 80% sulphuric acid solution are then added, at 20°C.

The solvent is distilled off, the mixture cooled to a temperature of 0 to -5°C and the crystals separated by filtration on a Büchner flask to obtain,

after drying, 779.1 kg of clopidogrel hydrogen sulphate Form 1; m.p. = 184 ±3°C.

The resulting aqueous-acetone mother liquors at a temperature of less than 40°C subsequently release, after 3 to 6 months, crystals of clopidogrel hydrogen sulphate Form 2; m.p. = 176 ± 3°C.

EXAMPLE 1 C

1200 kg of clopidogrel camphorsulphonate prepared as indicated above are introduced into a 6000 litres reactor, under nitrogen. 2345 litres of dichloromethane are added and the reaction mixture is stirred for 30 minutes to 1 hour. Then a solution of 214.5 kg of potassium carbonate dissolved in 1827 litres of deionized water is introduced. The organic phase is drawn off and the aqueous phase is washed several times with dichloromethane. The organic phases are combined and concentrated under vacuum. Acetone is added to the concentrate and the mixture is filtered on a cartridge filter of 0.1 μ to 1 μ. The acetone solution (3033 litres) containing the base is loaded into a reactor under nitrogen and 264.8 kg of a 96% sulphuric acid solution are then added, at 20°C.

The solvent is distilled off, the mixture cooled to a temperature of 0 to -5°C and the crystals separated by filtration on a Büchner flask to obtain, after drying, 785.3 kg of clopidogrel hydrogen sulphate Form 1; m.p. = 184 ±3°C.

The resulting aqueous-acetone mother liquors at a temperature of less than 40°C subsequently release, after 3 to 6 months, crystals of clopidogrel hydrogen sulphate Form 2; m.p. = 176 ± 3°C.

EXAMPLE 2

909 litres of dichloromethane and 450 kg of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate are loaded into a reactor. The camphorsulphonic acid is extracted with an aqueous solution of 80 kg of potassium carbonate in 680 litres of water. The organic phase is then washed with water. The dichloromethane is concentrated and the concentration residue is taken up in 1140 litres of acetone. 100 kg of 96% sulphuric acid are then added at 20°C. The mixture is seeded with 0.3 kg of clopidogrel hydrogen sulphate Form 2 obtained according to EXAMPLE 1B or 1C. The clopidogrel hydrogen sulphate crystallizes out. The material is filtered and then washed with acetone and dried under reduced pressure. 310 kg of clopidogrel hydrogen sulphate Form 2 are obtained, that is a yield of 90.9%; m.p. = 176 ± 3°C.

EXAMPLE 3

909 litres of dichloromethane and 450 kg of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate are loaded into a reactor. The

camphorsulphonic acid is extracted with an aqueous solution of 80 kg of potassium carbonate in 680 litres of water. The organic phase is then washed with water. The dichloromethane is concentrated and the concentration residue is taken up in 1296 litres of acetone.

The temperature is stabilized at 20°C and the Turrax® is switched on. 10% of the quantity of 94-96% sulphuric acid (8.3 kg) is then added within a few minutes. The mixture is seeded with 0.012 kg of clopidogrel hydrogen sulphonate Form 2 obtained according to EXAMPLE 1B or 1C. The clopidogrel hydrogen sulphonate crystallizes out. The reaction mixture is left under the action of the Turrax® for 45 minutes. The remaining 90% of 94-96% sulphuric acid (74.6 kg) is then poured in within about 2 hours, while the Turrax® is kept in operation. The Turrax® is stopped 30 min after the end of the addition of acid and the mixture is stirred for 30 minutes at 20°C. It is filtered, washed with acetone and dried under reduced pressure.

310 kg of clopidogrel hydrogen sulphonate Form 2 are obtained, that is a yield of 90.9%, m.p. = 176 ± 3°C.

CLAIMS

1. Crystalline (+)-(S) polymorph of clopidogrel hydrogen sulphate (Form 2) whose powder X-ray diffractogram shows the following characteristic peaks expressed as interplanar distances at approximately 4.11; 6.86; 3.60; 5.01; 3.74; 6.49; 5.66 Å.

2. Crystalline (+)-(S) polymorph of clopidogrel hydrogen sulphate (Form 2) whose infrared spectrum exhibits characteristic absorptions expressed in cm^{-1} at: 2551, 1497, 1189 and 1029, with respective percentages of transmittance of about: 43; 63.7; 18; 33.2.

3. Crystalline (+)-(S) polymorph of clopidogrel hydrogen sulphate (Form 2) having a melting point of 176 ± 3°C.

4. Crystalline polymorph of clopidogrel hydrogen sulphate (Form 2) characterized by the powder X-ray diffractogram according to Figure 2.

5. Crystalline polymorph of clopidogrel hydrogen sulphate (Form 2) characterized by an infrared spectrum according to Figure 3.

6. Crystalline polymorph of clopidogrel hydrogen sulphate (Form 2) characterized by the powder X-ray diffractogram according to Claim 1 and an infrared spectrum according to Claim 2.

7. Method for the preparation of (+)-(S)-clopidogrel hydrogen sulphate Form 2, according to Claims 1, 2 and 3, characterized in that: the aqueous-acetone mother liquors resulting from the crystallization of (+)-(S)-clopidogrel hydrogen sulphate Form 1 undergo salting out in order to obtain, after 3 to 6 months, crystals of clopidogrel hydrogen sulphate Form 2.

8. Method according to Claim 7, characterized in that the aqueous-acetone mother liquors resulting from the crystallization of (+)-(S)-clopidogrel hydrogen sulphate Form 1 contain 0.3 to 1% of water.

9. Method according to Claim 7, characterized in that the aqueous-acetone mother liquors resulting from the crystallization of (+)-(S)-clopidogrel hydrogen sulphate Form 1 contain up to about 10% of clopidogrel hydrogen sulphate, this quantity being calculated from the quantity of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate used during the conversion to hydrogen sulphate.

10. Method according to any one of Claims 7 to 9, characterized in that the aqueous-acetone mother liquors resulting from the crystallization of (+)-(S)-clopidogrel hydrogen sulphate Form 1 release slowly,

after a period of three to six months, at a temperature of less than 40°C, clopidogrel hydrogen sulphate Form 2.

11. Method for the preparation of clopidogrel hydrogen sulphate Form 2 in which:

(a) methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl-5-acetate camphorsulphonate is dissolved in an organic solvent,

(b) camphorsulphonic acid is extracted with an aqueous alkaline solution of potassium carbonate and washed with water,

(c) the organic phase is concentrated under reduced pressure and the concentration residue is taken up in acetone,

characterized in that 94-96% sulphuric acid is added and the mixture is seeded with clopidogrel hydrogen sulphate Form 2, the product is crystallized, the mixture is cooled, filtered and the crystals are washed and then dried under reduced pressure to give clopidogrel hydrogen sulphate Form 2.

12. Pharmaceutical composition containing, as active ingredient, the Form 2 polymorph of clopidogrel hydrogen sulphate according to Claim 1 in combination with at least one pharmaceutical excipient.

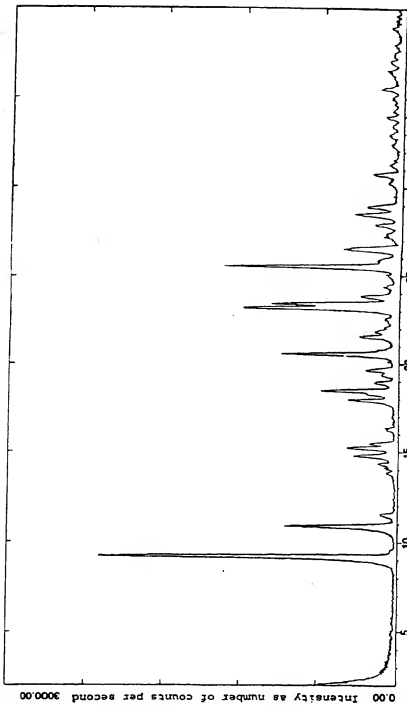


FIGURE 1

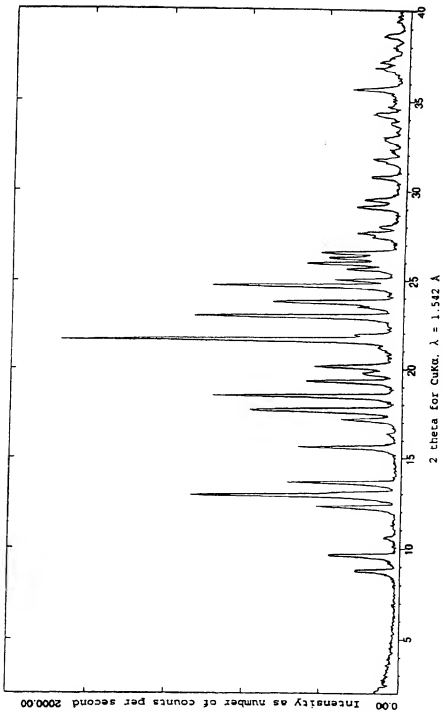


FIGURE 2

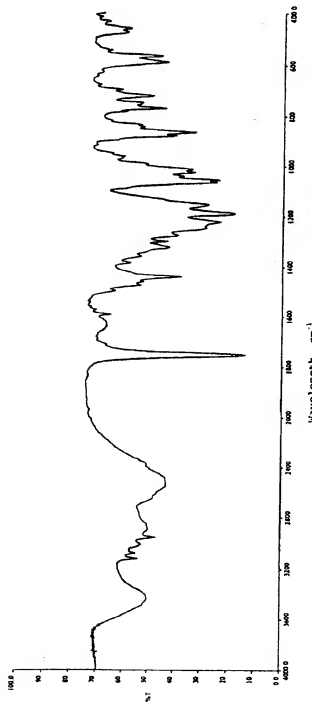


FIGURE 3

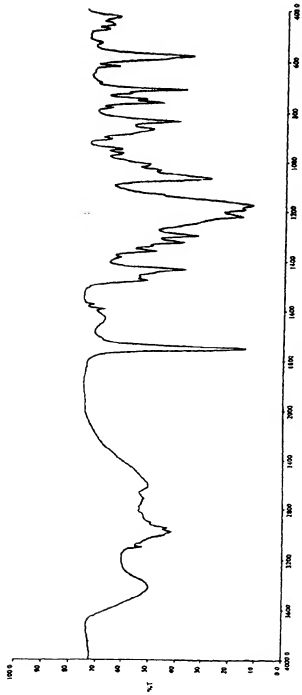
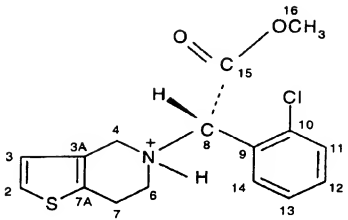


FIGURE 4



, HSO_4^-

FIGURE 5

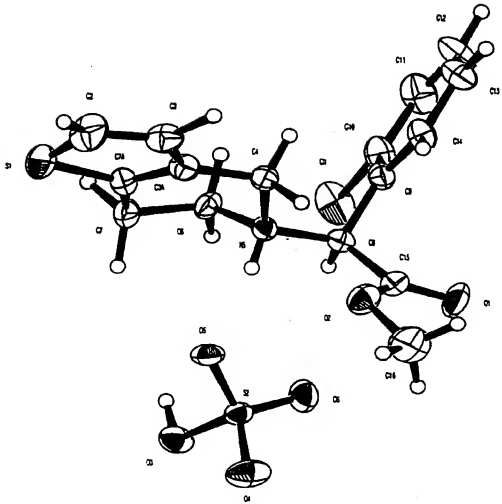


FIGURE 6

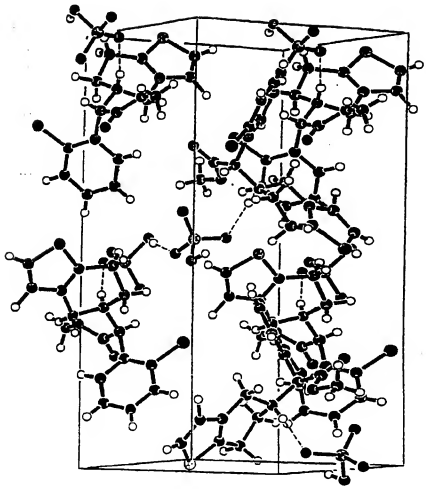


FIGURE 7